

## **REMARKS**

All outstanding requirements will now be addressed in the order they appear in the Office Action mailed July 14, 2009.

### ***Restriction***

1. In the Office action of March 16, 2009, election of a single disclosed species was required under 35 U.S.C. 121 and 371. In Applicant's reply of April 30, 2009, a provisional election of a single disclosed species was made with traverse, the single disclosed species being a process for making a Donepezil derivative of formula (I), wherein R<sub>1</sub> represents hydrogen, R<sub>2</sub> represents methoxy, R<sub>3</sub> represents methoxy, R<sub>4</sub> represents hydrogen, R<sub>5</sub> represents phenyl, and n is 0. In the Office action of July 14, 2009, the requirement for restriction was made FINAL.

Upon allowance of a generic claim, the Examiner is respectfully requested to consider claims to additional species which depend or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. See, MPEP 809.02(a).

In addition, if after this response is entered, this application becomes in condition for allowance except for the presence of claims directed to an invention non-elected with traverse, the Examiner is respectfully requested to give Applicant one month or thirty days, whichever is longer, to cancel such claims or take other appropriate action (37 CFR 1.144). See, MPEP 821.01.

### ***Priority***

2. This application is a National Stage Application of International Patent Application No. PCT/CN 2004/001227, with an international filing date of October 28, 2004, which is based on Chinese Patent Application No. 200310106920.3, filed November 5, 2003.

In the Office action of July 14, 2009, the Examiner requested that Applicant provide a certified English version of the foreign priority documents. Applicant has provided the same herewith.

In light thereof, the Examiner is respectfully requested to confirm that the formal requirements for securing the right of priority to the foreign application have been complied with.

In addition, Applicant respectfully submits that in the absence of the requested translation of the foreign priority document, the accorded priority date should still be Oct. 28, 2004 (which is the PCT filing date) and not, as stated by the Examiner, Apr. 30, 2006, which is merely the 371(c) date. The English translation of the PCT application is of record, and that is what is presently being examined.

***Claim Rejections – 35 USC § 112***

3. Claims 1 stands rejected under 35 U.S.C. 112, second paragraph, as being “incomplete for omitting essential elements, such as reagents, solvents, and conditions etc. therefore rendered the claims with unclear and indefinite conditions of the process.” The Examiner further alleges that the term alkylation is not limited to “N” alkylation and no reagents for forming the particular alkylated product has been pointed out.

Without acquiescing in the rejection, Applicant has amended claim 1, without prejudice, to include additional reagents, solvents, and conditions. In addition, Applicant submits that because N-alkylated product is formed in claim 1 (see formula (I)), there is no ambiguity as to whether the alkylation is an N or a C-alkylation. Withdrawal of the rejection is respectfully requested.

4. Claims 1-6, 11-22 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner appears to argue that a skilled artisan would not know how to make the various starting materials of formula (II), wherein  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  each independently represents H, F, an alkyl having from 1 to 4 carbon atoms, or an alkoxy having from 1 to 4 carbon atoms.

Applicant denies that claims 1-6 and 11-22 are not enabled and respectfully requests reconsideration. Specifically, Applicant submits that at least the following compounds of formula (II) are known from the literature, and many of these are commercially available:

$R^1$	$R^2$	$R^3$	$R^4$	Name
H	H	H	H	1-indanone
H	H	H	CH <sub>3</sub>	4-methyl-1-indanone
CH <sub>3</sub>	H	H	H	7-methyl-1-indanone
H	CH <sub>3</sub>	H	H	6-methyl-1-indanone
H	F	H	H	6-fluoro-1-indanone
H	H	F	H	5-fluoro-1-indanone
CH <sub>3</sub>	H	CH <sub>3</sub>	H	5,7-dimethyl-1-indanone
OH	H	H	CH <sub>3</sub>	7-hydroxy-4-methyl-1-indanone
OH	CH <sub>3</sub>	H	H	7-hydroxy-6-methyl-1-indanone
H	CH <sub>3</sub>	H	OH	4-hydroxy-7-methyl-1-indanone
F	H	F	H	5,7-difluoro-1-indanone
OCH <sub>3</sub>	H	OCH <sub>3</sub>	H	5,7-dimethoxy-1-indanone
H	OCH <sub>3</sub>	OCH <sub>3</sub>	H	5,6-dimethoxy-1-indanone
H	H	OCH <sub>3</sub>	OCH <sub>3</sub>	4,5-dimethoxy-1-indanone
OCH <sub>3</sub>	H	H	OCH <sub>3</sub>	4,7-dimethoxy-1-indanone
OCH <sub>3</sub>	OCH <sub>3</sub>	H	Br	4-bromo-6,7-dimethoxy-1-indanone
OH	OCH <sub>3</sub>	H	Br	4-bromo-7-hydroxy-6-methoxy-1-indanone
CH <sub>3</sub>	CH <sub>3</sub>	H	CH <sub>3</sub>	2,2,4,6,7-pentamethyl-1-indanone
CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	2,2,5,6,7-pentamethyl-1-indanone
OCH <sub>3</sub>	H	OCH <sub>3</sub>	OCH <sub>3</sub>	4,5,6-trimethoxy-1-indanone
OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	5,6,7-trimethoxy-1-indanone
CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	2,3,4,5,6,7-hexamethyl-1-indanone

The compounds of formula (II), including those that are tetrasubstituted, can be prepared following, e.g., the procedure described by Ready et al. Journal of Organometallic Chemistry, 583(1999), 11-27. See also, WO2000075114 (published 12/14/2000). In addition,

compounds of formula (I), wherein  $R^1$ ,  $R^2$ , and  $R^3$  are methoxy,  $R^4$  is hydrogen and  $R^5$  is phenyl, have been synthesized by Sugimoto et al., J. Med. Chem. 1995, 38,4821-4829.

While the Examiner alleges that only limited members of the generic scope were known, the presence of limited working examples (or even only one working example) should never be the sole reason for rejecting claims being broader than the enabling disclosure. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate the limited working examples (or that one example) across the entire scope of the claims. See, MPEP 2164.03.

Since the claims are of rather limited scope ( $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  are restricted only to H, F,  $C_{1-4}$  alkyl, or  $C_{1-4}$  alkoxy) and since a variety of similar starting materials falling within the scope of Applicant's Markush structure for the starting material is known in the art, it is clear and convincing that experimentation would not be undue and that the claims are enabled. (See, MPEP 2164.01, "A patent need not teach, and preferably omits, what is well known in the art.")

In light thereof, withdrawal of the enablement rejection is respectfully requested.

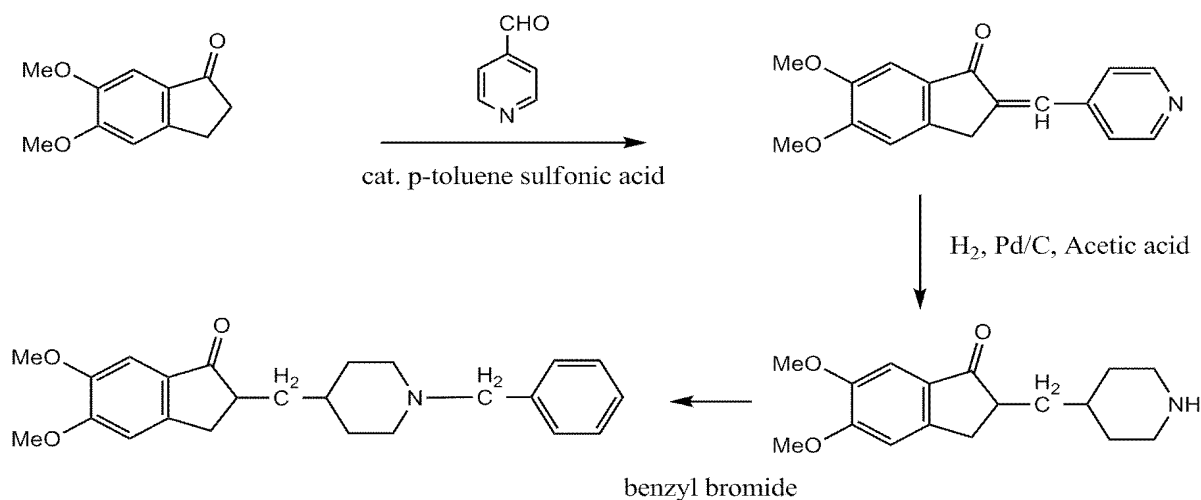
### ***Claim Rejections – 35 USC § 102***

5. Claims 1-2, 4-6, and 11-22 stand rejected under 35 U.S.C. 102(e) as being allegedly anticipated by Reddy et al. (US Pat 7,148,354).

Applicant respectfully disagrees with the rejection, denies that that claims 1-2, 4-6, and 11-22 are anticipated by Reddy, and respectfully requests reconsideration and withdrawal of the rejections.

Applicants submit that Reddy recites a process for the preparation of denepezil, as illustrated below in **Scheme 1**, including: a) refluxing the mixture of 5,6-dimethoxy-2,3-dihydro-1H-

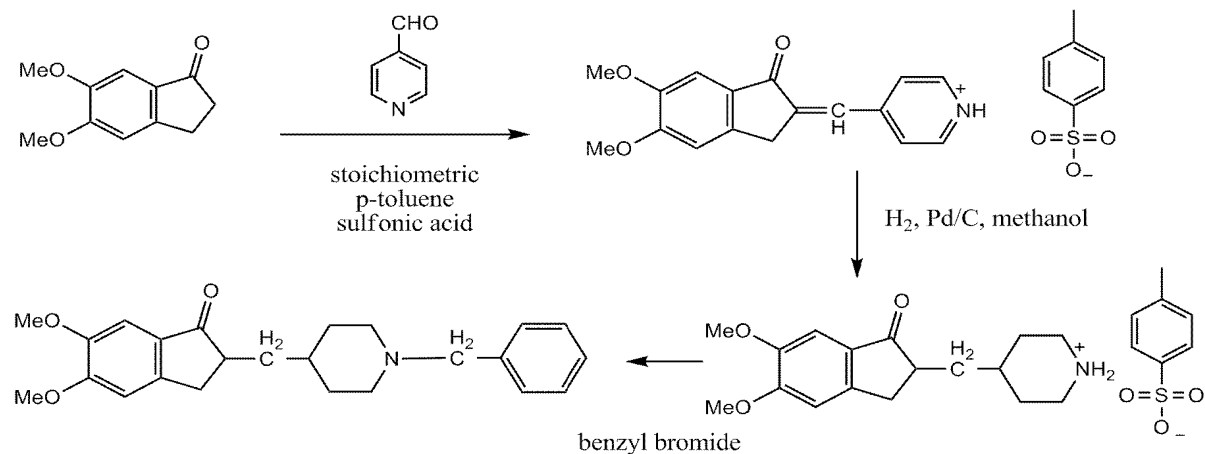
inden-1-one and pyridine-4-carboxaldehyde in the presence of a *catalytic* amount of p-toluene sulfonic acid; b) basifying the solid obtained in step (a) to afford **5,6-dimethoxy-2-(pyridin-4-ylmethylene)-2,3-dihydro-1H-inden-1-one**; c) reducing 5,6-dimethoxy-2-(pyridin-4-ylmethylene)-2,3-dihydro-1H-inden-1-one in presence of acetic acid and palladium on carbon; d) removing the catalyst and basifying the residue to afford **5,6-dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydro-1H-inden-1-one**; and e) reacting 5,6-dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydro-1H-inden-1-one with benzyl bromide to obtain 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one.



**Scheme 1**

However, one embodiment of the process invented by Applicant, as illustrated below in **Scheme 2**, comprises: a) reacting 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one and pyridine-4-carboxaldehyde in the presence of a *stiochiometric* amount of p-toluene sulfonic acid to obtain **4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate**; b) reducing 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate with H<sub>2</sub> using palladium on carbon in methanol to afford **4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)piperidinium 4-methylbenzenesulfonate**; and c) reacting 4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)piperidinium 4-methylbenzenesulfonate with H<sub>2</sub> and

benzyl bromide in the presence of a base and a metal catalyst to yield 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one.



**Scheme 2**

Applicant's process is simpler and more environmentally friendly in that the product in the first step is a tosylate, which allows the salt to precipitate out at the completion of the reaction. The neutralization and extraction steps, both of which are required in Reddy, can be omitted in Applicant's process and the solvent can be reused. Similarly, the product of the second steps is also a tosylate, which allows the salt to precipitate out at the completion of the reaction and allows the neutralization and extraction steps, both of which are required in Reddy, to be omitted and solvent to be re-used.

Tosic acid is used by Applicant in stoichiometric and more-than-stoichiometric amounts both as a reagent and as catalyst, while Reddy uses tosic acid in a catalytic amount in the first step only, and uses acetic acid in the following step. Applicant has discovered that only strong acid is suitable in methods of the invention because a weak acid (such as acetic acid) will give a mixture of free base and salt, which is very difficult to crystallize, and instead, produces a thick oil, making purification very difficult. Therefore, Applicant only claims a strong acid as part of the reaction conditions. A strong acid is not claimed or recited by Reddy for all of its steps.

The intermediates in the Applicant's process, i.e., compounds of formula (III) and formula (IV) are not the intermediates in Reddy's process. In fact, to the best of Applicant's knowledge, the compounds of formula (III) and formula (IV) have been first prepared and fully characterized by Applicant (and their CAS numbers were first assigned in connection with Applicant's invention).

In sum, the two processes are clearly different, and Reddy does not anticipate the instant claims.

In addition, Applicant respectfully submits that the 35 U.S.C. 102(b) rejection is improper as a matter of law because the Examiner has not made a prima facie case for anticipation, as the Examiner has not met the burden of establishing by preponderance of evidence that the reference teaches each and every element of the claimed invention, arranged as in the claims. Specifically, in deciding the issue of anticipation, "the trier of fact must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference" Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co. 730 F.2d 1452, 221 USPQ 481, 485 (Fed. Cir. 1984) citing Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983). A two-line rejection by the Examiner does not meet this burden.

For all of the reasons presented above, Applicant respectfully requests that the anticipation rejection be withdrawn.

### ***Claim Rejections – 35 USC § 103***

6. Claims 1-2, 4-6, and 11-22 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Lensky (US 5,606,064) in view of Devries '584 (WO 97/22584). The Examiner alleges that Lensky recites "very similar steps" except that "instead of alkylation being performed at the last step, it was performed before hydrogenation." The Examiner

further alleges that since Devries '584 discloses alkylation after hydrogenation, changing the sequence of steps would have been obvious.

Applicant respectfully disagrees with the rejection, denies that that claims 1-2, 4-6, and 11-22 are obvious over Lensky in view of Devries '584, and respectfully requests reconsideration and withdrawal of the rejections.

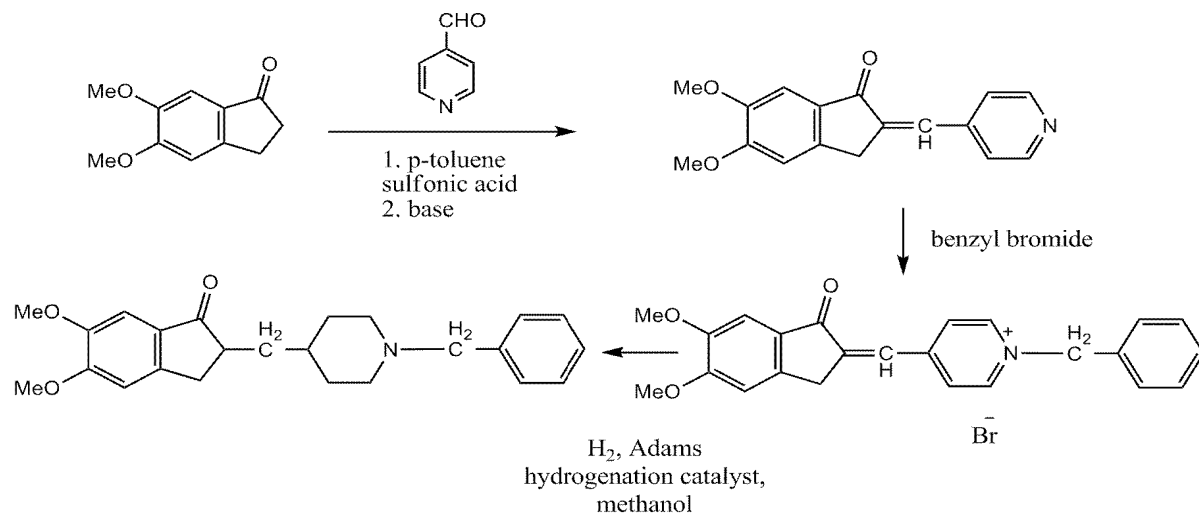
The factual determinations underpinning the legal conclusion of obviousness include: 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. See, Esai Co., Ltd. v. Dr. Reddy's Laboratories, Ltd., 533 F.3d 1353 (Fed. Cir. 2008) citing Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966).

#### The Scope and Content of the Prior Art

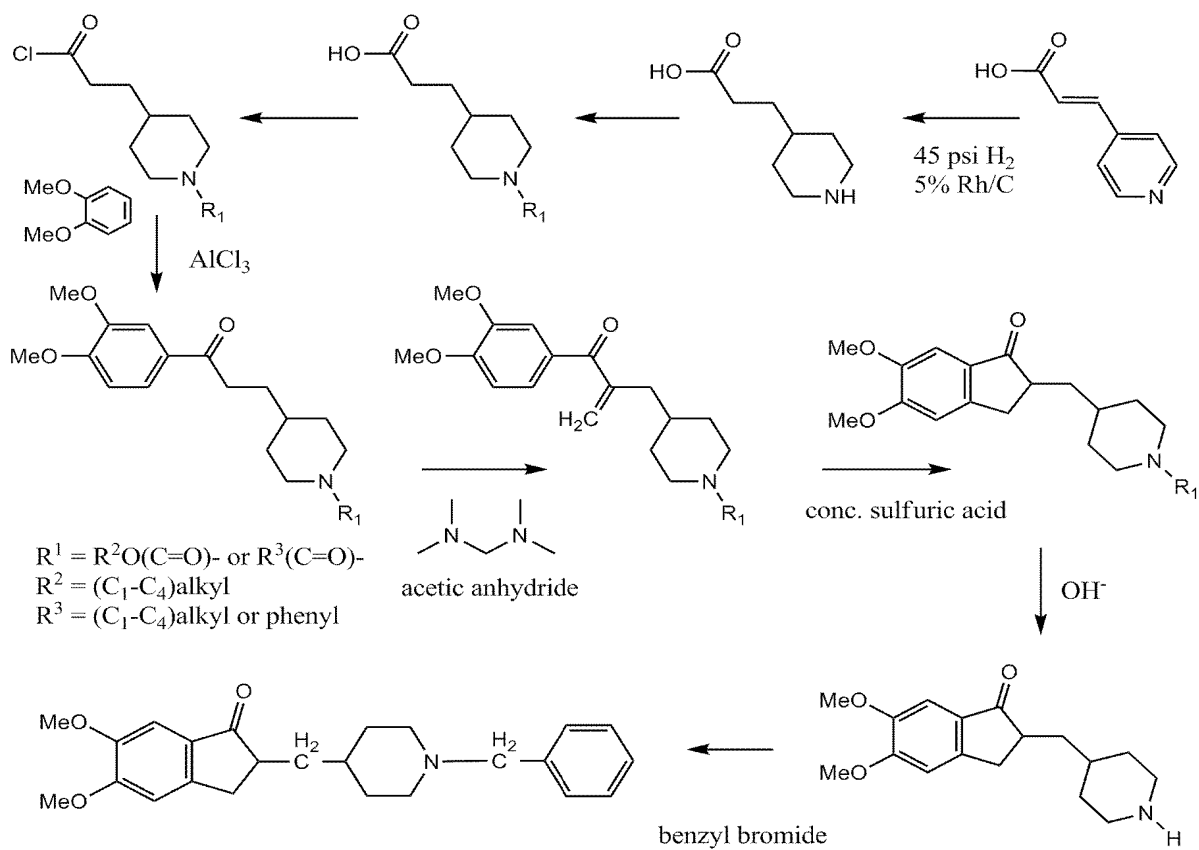
Lensky recites a process for the preparation of denepezil, as illustrated below in **Scheme 3**, including: a) reacting 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one with pyridine-4-aldehyde to yield 5,6-dimethoxy-2-(pyridin-4-ylmethylene)-2,3-dihydro-1*H*-inden-1-one, b) reacting 5,6-dimethoxy-2-(pyridin-4-ylmethylene)-2,3-dihydro-1*H*-inden-1-one with benzyl bromide to form 1-benzyl-4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium bromide, and c) hydrogenating 1-benzyl-4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium bromide to form 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one.

Devries '584 recites a process for the preparation of donepezil, as illustrated below in **Scheme 4**, including: a) hydrogenating 3-pyridin-4-ylpropen-2-oic acid to yield 3-piperidin-4-ylpropanoic acid, (b) reacting 3-piperidin-4-ylpropanoic acid with methyl chloroformate to yield 3-[N-(Methoxycarbonyl)-piperidin-4-yl]propionic acid; c) converting 3-[N-(Methoxycarbonyl)-piperidin-4-yl]propionic acid to 4-(2-chlorocarbonyl-ethyl)-piperidine-1-





**Scheme 3**



**Scheme 4**

carboxylic acid methyl ester; d) reacting 4-(2-chlorocarbonyl-ethyl)-piperidine-1-carboxylic acid methyl ester with 1,2-dimethoxybenzene in the presence of aluminum chloride to 4-[3-(3,4-dimethoxy-phenyl)-3-oxo-propyl]-piperidine-1-carboxylic acid methyl ester; e) converting 4-[3-(3,4-dimethoxy-phenyl)-3-oxo-propyl]-piperidine-1-carboxylic acid methyl ester to 4-[2-(3,4-dimethoxy-benzoyl)-allyl]-piperidine-1-carboxylic acid methyl ester; f) converting 4-[2-(3,4-dimethoxy-benzoyl)-allyl]-piperidine-1-carboxylic acid methyl ester to 4-(5,6-dimethoxy-1-oxo-indan-2-ylmethyl)-piperidine-1-carboxylic acid methyl ester; g) converting 4-(5,6-dimethoxy-1-oxo-indan-2-ylmethyl)-piperidine-1-carboxylic acid methyl ester with potassium hydroxide to yield 5,6-dimethoxy-2-piperidin-4-ylmethyl-indan-1-one; and h) reacting 5,6-dimethoxy-2-piperidin-4-ylmethyl-indan-1-one with benzyl bromide to yield 2-(1-benzyl-piperidin-4-ylmethyl)-5,6-dimethoxy-indan-1-one.

#### The Level of Ordinary Skill in the Art

A person of ordinary skill in the art with respect to the pending claims is a chemist. Ordinary skill in the chemical arts is generally low. In general, and apart from special circumstances, chemists cannot accurately and unambiguously predict outcomes of chemical reactions without undue experimentation, especially those chemical reactions that involve complex chemical compounds having multiple functional groups. This is to say also that the chemical arts are often unpredictable. See, e.g., *Eisai* at 1359 (Fed. Cir. 2008) (“To the extent an art is unpredictable, as the chemical arts often are [...]”).

#### The Differences between the Claimed Invention and the Related Art

Because the references at issue recite chemical compounds that undergo chemical reactions, the analysis of the differences between the claimed invention and the prior art turns here *inter alia* on the structural similarities and differences between compounds used in the claimed process and compounds used in processes recited in the references cited. Cf. *Eisai* at 1359 (Fed. Cir. 2008) quoting *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006) (noting that, for a chemical compound, a prima facie case of

obviousness requires “structural similarity between claimed and prior art subject matter ... where the prior art gives reason or motivation to make the claimed compositions” (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))).

Obviousness based on structural similarity of a chemical process thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known process in a particular way to achieve the claimed process. Cf. Eisai at 1359 (Fed. Cir. 2008) quoting Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007).

The differences between Applicants’ process as claimed, and the processes recited in the references cited are many, and include the following:

(a) In Lensky, benzyl bromide is reacted with 5,6-dimethoxy-2-(pyridin-4-ylmethylene)-2,3-dihydro-1H-inden-1-one to yield 1-benzyl-4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium bromide, which is then isolated and hydrogenated, while in one embodiment of Applicant’s process, 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate is hydrogenated and then the resultant 4-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)piperidinium 4-methylbenzenesulfonate is reacted *in situ* with benzyl bromide. There is no mention anywhere in Lensky that forming 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate as the intermediate and subjecting this compound to hydrogenation would be beneficial. In fact, Lensky teaches away from forming 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate, because Lensky forms this compound and immediately converts it to the free 5,6-dimethoxy-2-(pyridin-4-ylmethylene)-2,3-dihydro-1H-inden-1-one before proceeding further. There is also no mention anywhere in Lensky that the reaction of 4-((5,6-dimethoxy-1-oxo-1H-inden-2(3H)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate with benzyl bromide and the subsequent hydrogenation would run *in situ*. Thus, there is no motivation and no expectation of success to modify the process by Lensky as proposed by the Examiner to arrive at the process as claimed by Applicant.

(b) In Devries '584, hydrogenation occurs at the stage of 3-pyridin-4-ylpropen-2-oic acid rather than as in Applicant's process at the stage of 4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate. 3-pyridin-4-ylpropen-2-oic acid is much different than 4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate. The former is an  $\alpha$ ,  $\beta$ -unsaturated carboxylic *acid* conjugated to an aromatic pyridine ring, while the latter is a tosylate *salt* of an indanone conjugated to a pyridinium cation. Because the reactivities of the two species are much different, a skilled artisan would not be able to conclude after reading Devries '584 that 4-((5,6-dimethoxy-1-oxo-1*H*-inden-2(3*H*)-ylidene)methyl)pyridinium 4-methylbenzenesulfonate could be successfully hydrogenated, nor that it could be successfully hydrogenated and then reacted *in situ* with benzyl bromide to form 2-(1-benzyl-piperidin-4-ylmethyl)-5,6-dimethoxy-indan-1-one in one pot. In addition, while Devries '584 hydrogenates 3-pyridin-4-ylpropen-2-oic acid using rhodium on carbon Applicant uses platinum or palladium, and while Devries '584 uses 45 psi hydrogen pressure, Applicant uses less than 15 psi. Devries '584 teaches away from "changing the sequence of steps" because when doing so, harsher hydrogenation conditions would likely need to be used and lower yields would likely be obtained. Thus, there is no motivation and no expectation of success to modify the process by Lensky as proposed by the Examiner to arrive at the process as claimed by Applicant.

Although these differences between Lensky-Devries '584 and the Applicant's invention as claimed are crucial and involve much different compounds, reagents, and intermediates, the Examiner readily dismissed them as simply changing the sequence of hydrogenation and alkylation and mere picking and choosing of an effect oriented parameter for maximum product yield. This position is untenable. Specifically, Applicant submits that where steps carried out in a process are sequential chemical reactions (rather than physical processes), "changing the sequence of steps" would require a substantial reconstruction and redesign and inclusion of additional steps and reagents to yield the same products. This is to say also, that the Examiner improperly refers to Applicant's process as a mere changing the sequence of steps because not only the steps are different but the chemical intermediates themselves are

also different. Where there is no motivation to change intermediates, changing intermediates does in fact result in a non-obvious process, especially where there is no expectation of success with respect to applying reagents to different classes of compounds.

In light thereof, Applicants respectfully request reconsideration and withdrawal of the obviousness rejections over the claims as amended.

#### Evidence of Secondary Factors

While a prima facie case of obviousness has not been established, Applicants wish to argue in the alternative the following secondary factors.

#### ***Unexpected and superior results***

Applicants' steps of converting 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one to 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one are carried out in an overall greater than 90% yield. Lensky's yield for converting 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one to 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one is less than 60%. This over 30% difference in yields is clearly superior and unexpected. It is also unexpected and superior that Applicant can run its steps in situ and that fewer steps overall are necessary as compared with Lensky-Devries. These unexpected and superior results weight heavily in favor of finding Applicants' process non-obvious.

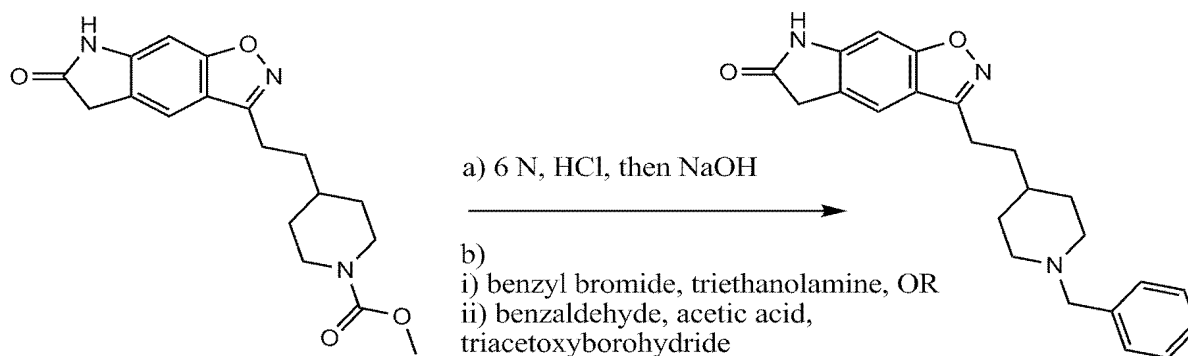
7. Claims 1-6, and 11-22 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Lensky in view of Devries '584 (WO 97/22584) and further in view of US Pat. No. 5,916,902 to Devries ("Devries '902").

The Examiner alleges that Lensky recites "very similar steps" except that "instead of alkylation being performed at the last step, it was performed before hydrogenation." However, the Examiner further alleges that since Devries '584 discloses alkylation after hydrogenation, and since Devries '902 suggested that N-benylation can be carried out by a

benzylating agent or benzaldehyde in the presence of a reducing agent, changing the sequence of steps would have been obvious.

Applicant respectfully disagrees with the rejection, denies that that claims 1-6, and 11-22 are obvious over Lensky in view of Devries '584 and further in view of Devries '902, and respectfully requests reconsideration and withdrawal of the rejections.

Applicant re-alleges the arguments made in item 6, above with respect to claims 1-2, 4-6, and 11-22. Further, Applicant respectfully submits that a skilled artisan after considering Devries '902 in addition to Lensky and Devries '584 would still not arrive at Applicant's invention because Devries '902 applies benzyl halide and base or benzaldehyde in the presence of a reducing agent to much different intermediate than that in the processes claimed by Applicant. Specifically, as illustrated below in **Scheme 5**, Devries '902 converts an 5H-isoxazolo[4,5-f]indol-6(7H)-one rather than a 2,3-dihydro-1H-inden-1-one.



**Scheme 5**

There is no mention anywhere in the references cited that substituting the 5H-isoxazolo[4,5-f]indol-6(7H)-one of Devries '902 for the 2,3-dihydro-1H-inden-1-one core of Lensky would be beneficial. In addition, Devries '902 does not use H<sub>2</sub> as the hydrogenation reagent, and Devries '902 does not suggest that H<sub>2</sub> could be used in situ with benzyl bromide. Thus, there

is no motivation and no expectation of success to modify the process by Lensky as proposed by the Examiner to arrive at the process as claimed by Applicant.

In light thereof, Applicants respectfully request reconsideration and withdrawal of the obviousness rejections over the claims as amended.

While a prima facie case of obviousness has not been established, Applicant wishes to argue in the alternative the secondary factors as above in item 6.

8. Claims 1-6, and 11-22 stand rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Reddy in view of Devries '902. The Examiner alleges that Reddy discloses "anticipatory process" wherein N-alkylation was performed with benzyl bromide. The Examiner admits that Reddy does not recite "using benzaldehyde instead of benzylbromide", but the Examiner concludes, in essence, that since Devries '902 suggest using benzaldehyde instead of benzylbromide as an optional choice, prima facie case of obviousness exists.

Applicant respectfully disagrees with the rejection, denies that that claims 1-6, and 11-22 are obvious over Reddy in view of Devries '902, and respectfully requests reconsideration and withdrawal of the rejections.

The factual determinations underpinning the legal conclusion of obviousness include: 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness. See, Esai Co., Ltd. v. Dr. Reddy's Laboratories, Ltd., 533 F.3d 1353 (Fed. Cir. 2008) citing Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966).

#### The Scope and Content of the Prior Art

Reddy recites a process for the preparation of denepezil, as illustrated below in **Scheme 1**, above. Devries '902 recites a process for the preparation of 5,7-dihydro-3-[2-(1-benzylpiperidin-4-yl)ethyl]-6H-pyrrolo-[4,5-F]-1,2-benzisoxazol-6-one, as partially illustrated in **Scheme 5**, above.

#### The Level of Ordinary Skill in the Art

A person of ordinary skill in the art with respect to the pending claims is a chemist. Ordinary skill in the chemical arts is generally low. In general, and apart from special circumstances, chemists cannot accurately and unambiguously predict outcomes of chemical reactions without undue experimentation, especially those chemical reactions that involve complex chemical compounds having multiple functional groups. This is to say also that the chemical arts are often unpredictable. See, e.g., Eisai at 1359 (Fed. Cir. 2008) (“To the extent an art is unpredictable, as the chemical arts often are [...]”).

#### The Differences between the Claimed Invention and the Related Art

Because the references at issue recite chemical compounds that undergo chemical reactions, the analysis of the differences between the claimed invention and the prior art turns here *inter alia* on the structural similarities and differences between compounds used in the claimed process and compounds used in processes recited in the references cited. Cf, Eisai at 1359 (Fed. Cir. 2008) quoting Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1377 (Fed. Cir. 2006) (noting that, for a chemical compound, a prima facie case of obviousness requires “structural similarity between claimed and prior art subject matter ... where the prior art gives reason or motivation to make the claimed compositions” (quoting In re Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))).

Obviousness based on structural similarity of a chemical process thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select



and then modify a known process in a particular way to achieve the claimed process. Cf. Eisai at 1359 (Fed. Cir. 2008) quoting Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007).

The differences between Applicants' process as claimed, and the processes recited in the references cited are many, and include the following:

Applicant's process is simpler and more environmentally friendly in that the product in the first step is a tosylate, which allows the salt to precipitate out at the completion of the reaction. The neutralization and extraction steps, both of which are required in Reddy, can be omitted in Applicant's process and the solvent can be reused. Similarly, the product of the second steps is also a tosylate, which allows the salt to precipitate out at the completion of the reaction and allows the neutralization and extraction steps, both of which are required in Reddy, to be omitted and solvent to be re-used.

Tosic acid is used by Applicant in stoichiometric and more-than-stoichiometric amounts both as a reagent and as catalyst, while Reddy uses tosic acid in a catalytic amount in the first step only, and uses acetic acid in the following step. Applicant has discovered that only strong acid is suitable in methods of the invention because a weak acid (such as acetic acid) will give a mixture of free base and salt, which is very difficult to crystallize, and instead, produces a thick oil, making purification very difficult. Therefore, Applicant only claims a strong acid as part of the reaction conditions. A strong acid is not claimed or recited by Reddy for all of its steps.

The intermediates in the Applicant's process, i.e., compounds of formula (III) and formula (IV) are not the intermediates in Reddy's process. In fact, to the best of Applicant's knowledge, the compounds of formula (III) and formula (IV) have been first prepared and fully characterized by Applicant (and their CAS numbers were first assigned in connection with Applicant's invention).

Further, Applicant respectfully submits that a skilled artisan after considering Devries '902 in addition to Reddy would still not arrive at Applicant's invention because Devries '902 applies benzyl halide and base or benzaldehyde in the presence of a reducing agent to much different intermediate than that in the processes claimed by Applicant. Specifically, as illustrated below in **Scheme 5**, Devries '902 converts an 5H-isoxazolo[4,5-f]indol-6(7H)-one rather than a 2,3-dihydro-1H-inden-1-one.

There is no mention anywhere in the references cited that substituting the 5H-isoxazolo[4,5-f]indol-6(7H)-one of Devries '902 for the 2,3-dihydro-1H-inden-1-one core of Reddy would be beneficial. In addition, Devries '902 does not use H<sub>2</sub> as the hydrogenation reagent, and Devries '902 does not suggest that H<sub>2</sub> could be used in situ with benzyl bromide or benzaldehyde. Thus, there is no motivation and no expectation of success to modify the process by Reddy as proposed by the Examiner to arrive at the process as claimed by Applicant.

In light thereof, Applicants respectfully request reconsideration and withdrawal of the obviousness rejections over the claims as amended.

#### Evidence of Secondary Factors

While a prima facie case of obviousness has not been established, Applicants wish to argue in the alternative the following secondary factors.

#### ***Unexpected and superior results***

Applicants' steps of converting 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one to 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one are carried out in an overall greater than 90% yield. Reddy's yield for converting 5,6-dimethoxy-2,3-dihydro-1H-inden-1-one to 2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one is less than 85%. In addition, 3-4 atmospheres of H<sub>2</sub> pressure are needed by Reddy, while Applicant uses only 1 atm, and Applicant's process is more environmentally friendly.

These differences are clearly superior and unexpected. It is also unexpected and superior that Applicant can run its steps in situ and that fewer steps overall are necessary as compared with Reddy-Devries. These unexpected and superior results weight heavily in favor of finding Applicants' process non-obvious.

### ***CONCLUSION***

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission only be charged to **Deposit Account No. 503182**.

Customer Number: **33,794**

Respectfully Submitted,

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